Dietary Fiber Intake and Risk of Colorectal Cancer

A Pooled Analysis of Prospective Cohort Studies

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Context Inconsistent findings from observational studies have continued the controversy over the effects of dietary fiber on colorectal cancer.

Objective To evaluate the association between dietary fiber intake and risk of colorectal cancer.

Design, Setting, and Participants From 13 prospective cohort studies included in the Pooling Project of Prospective Studies of Diet and Cancer, 725 628 men and women were followed up for 6 to 20 years across studies. Study- and sex-specific relative risks (RRs) were estimated with the Cox proportional hazards model and were subsequently pooled using a random-effects model.

Main Outcome Measure Incident colorectal cancer.

Results During 6 to 20 years of follow-up across studies, 8081 colorectal cancer cases were identified. For comparison of the highest vs lowest study- and sex-specific quintile of dietary fiber intake, a significant inverse association was found in the age-adjusted model (pooled RR=0.84; 95% confidence interval [CI], 0.77-0.92). However, the association was attenuated and no longer statistically significant after adjusting for other risk factors (pooled multivariate RR=0.94; 95% CI, 0.86-1.03). In categorical analyses compared with dietary fiber intake of 10 to <15 g/d, the pooled multivariate RR was 1.18 (95% CI, 1.05-1.31) for less than 10 g/d (11% of the overall study population); and RR, 1.00 (95% CI, 0.85-1.17) for 30 or more g/d. Fiber intake from cereals, fruits, and vegetables was not associated with risk of colorectal cancer. The pooled multivariate RRs comparing the highest vs lowest study- and sex-specific quintile of dietary fiber intake were 1.00 (95% CI, 0.90-1.11) for colon cancer and 0.85 (95% CI, 0.72-1.01) for rectal cancer (*P* for common effects by tumor site=.07).

Conclusions In this large pooled analysis, dietary fiber intake was inversely associated with risk of colorectal cancer in age-adjusted analyses. However, after accounting for other dietary risk factors, high dietary fiber intake was not associated with a reduced risk of colorectal cancer.

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DIETARY FIBER HAS BEEN HYpothesized to reduce the risk of colorectal cancer. Potential mechanisms for a protective effect include dilution of fecal carcinogens and procarcinogens, reduction of transit time of feces through the bowel, production of short chain fatty acids, which promote anticarcinogenic action, and binding of carcinogenic bile acids.[1] However, the results of numerous epidemiological studies have been inconsistent. Ecological correlation studies and many case-control studies have found an inverse association between dietary fiber intake and risk of colorectal cancer.[2] On

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the other hand, most prospective cohort studies have found no association between dietary fiber intake and risk of colorectal cancer[3-7] or adenomas (precursors of colorectal cancer),[8] and randomized clinical trials of dietary fiber supplementation have failed to show reductions in the recurrence of colorectal adenomas.[9-12] Recently, the European Prospective Investigation into Cancer and Nutrition (EPIC) study and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial observed a statistically significant 25% lower risk of colorectal cancer[13,14] or adenomas,[15] respectively, in the highest quintile of dietary fiber intake compared with the lowest. Because of these discordant results, the debate continues on whether dietary fiber consumption decreases colorectal cancer risk. In this study, we evaluated the association between dietary fiber intake and risk of colorectal cancer by reanalyzing the primary data from 13 prospective cohort studies.

METHODS

Study Population

The Pooling Project of Prospective Studies of Diet and Cancer (Pooling Project) was established to summarize the association between dietary factors and risk of cancers, and the details of the Pooling Project have been described previously.[16] For the colorectal cancer analyses, we identified 13 prospective cohort studies[3-6,17-25] that met the following inclusion criteria: (1) at least 50 incident colorectal cancer cases; (2) assessment of usual dietary intake; (3) completion of a validation study of the dietary assessment method or a closely related instrument; and (4) assessment of dietary fiber intake. Studies including men and women[6,18,19] were separated into sex-specific cohorts.

Dietary and Nondietary Assessment

Each study provided baseline intake data of foods and nutrients that were assessed by a study-specific food frequency questionnaire. We calculated energy-adjusted intakes using the residual method,[26] in which $\log_e$ transformed intake of each nutrient (excluding energy) was regressed against $\log_e$ transformed energy intake and then standardized to energy intakes of 2100 kcal/d for men and 1600 kcal/d for women. Pearson correlation coefficients between dietary fiber intake from the food frequency questionnaire and the reference method in the validation studies were higher than 0.50 in all studies.[27-36] Grain foods were categorized as either whole grain foods (>50% whole grain content) or refined grain foods (≤50% whole grain content).[37] We also received information on nondietary risk factors, which was collected by self-administered questionnaires at baseline in each study.

Case Ascertainment

Incident colorectal cancer cases were identified by each cohort through self-administered questionnaires with subsequent medical record review,[3,22,25] linkage with a cancer registry,[4,17-21] or both.[5,6,23,24] Some studies also had an additional linkage with a death registry.[3-6,17,19,21-24] The follow-up rate of these studies was generally over 90%.

Statistical Analysis

In addition to applying the exclusionary criteria used by each study, we also excluded individuals from the analyses who had a history of cancer other than nonmelanoma skin cancer at baseline and who reported implausible energy intakes (beyond 3 SDs from the study-specific $\log_e$-transformed mean energy intake).

Data analyses comprised study- and sex-specific analyses and subsequent pooled analyses of the study-specific results. Study- and sex-specific relative risks (RRs) and 2-sided 95% confidence intervals (CIs) were estimated with the Cox proportional hazards model.[38] SAS statistical software (version 8, SAS Institute Inc, Cary, NC)[39] was used for all studies except the Canadian National Breast Screening Study and the Netherlands Cohort Study, which were analyzed as case-cohort studies[40] using Epicure software (version 2.11, HiroSoft International Corp, Seattle, Wash).[41] Age at baseline (in years) and the year when the baseline questionnaire was returned were used as stratification variables, thereby creating a time metric that simultaneously accounted for age, calendar time, and time after entry into the study. Person-years of follow-up time were calculated from the date of the baseline questionnaire until the date of colorectal cancer diagnosis, death, or end of follow-up, whichever came first. The person-time experienced during the follow-up of the Nurses' Health Study was divided into 2 asymptotically uncorrelated segments[42] to take advantage of the more detailed dietary assessment in 1986. The RRs of colorectal cancer were estimated according to study-specific quintiles, as well as to categories defined by absolute intake cut points that were identical across studies. We performed study- and sex-specific age-adjusted and multivariate analyses. The proportion of missing values for each covariate measured in a study was generally less than 5%; an indicator variable for missing responses was created for each covariate in a study if needed. The test for trend across categories of intake was performed by assigning participants the median value of their category and entering those values as a continuous term in a regression model.

The pooled estimates and 95% CIs were calculated using a random-effects model that weighted individual study-specific $\log_e$ RRs by the inverse of the sum of their variance. Between-studies heterogeneity was tested by the Q statistic.[43] Differences in results among tumor sites were tested by the Wald test statistic.[44] A meta-regression model was used to test for variation in RRs by sex, geographical location of the study, and follow-up time.[45]

In addition, we evaluated whether dietary fiber intake was log-linearly associated with risk of colorectal cancer by comparing the nonparametric regression curve obtained using restricted cubic splines with the linear model using the likelihood ratio test and by visual in-

spection of the restricted cubic spline graphs.[46] For this analysis, all studies were combined into a single data set stratified by study, and the number and location of the knots were identified through a stepwise selection process.

The effect of misclassification of dietary fiber intake was evaluated by the method developed by Zucker and Spiegelman.[47]

RESULTS

During follow-up times of 6 to 20 years in 13 cohort studies, 7 328 414 person-years were accumulated and 8081 incident colorectal cancer cases were identified (2776 men and 5305 women; 5726 colon cancer and 2188 rectal cancer cases plus 167 site unspecified). Among the studies, median energy-adjusted dietary fiber intake ranged from 14 to 28 g/d in men and from 13 to 24 g/d in women. The major source of dietary fiber varied across studies with cereals as a major contributor to dietary fiber intake in the European studies, and fruits and vegetables as the main sources in the North American studies (TABLE 1).

In the age-adjusted model, dietary fiber intake was significantly associated with a 16% lower risk of colorectal cancer in the highest quintile compared with the lowest (pooled age-adjusted RR=0.84; 95% CI, 0.77-0.92) (TABLE 2). This association was attenuated slightly but still remained statistically significant after adjusting for nondietary risk factors, multivitamin use, and total energy intake (multivariate model I). Additional adjustment for dietary folate intake further weakened the association (multivariate model II). In the final model, which further adjusted for red meat, total milk, and alcohol intake, only a nonsignificant weak inverse association was found (pooled RR=0.94; 95% CI, 0.86-1.03; *P* for trend=.75; multivariate model III). There was no statistically significant heterogeneity between studies for the highest quintile indicating that the differences in the study-specific results were compatible with random variation (FIGURE 1). When we combined the studies into a single data set and analyzed associations using across-study sex-specific quintiles and adjusted for the same covariates in multivariate model III, the results were similar: compared with the lowest quintile (mean intake=11 g/d in men and 10 g/d in women), for quintile 2 (multivariate RR, 0.91; 95% CI, 0.84-0.99); for quintile 3 (multivariate RR, 0.98; 95% CI, 0.89-1.07); for quintile 4 (multivariate RR, 0.95; 95% CI, 0.86-1.04); and for quintile 5 (multivariate RR, 0.95; 95% CI, 0.86-1.06, mean intake=31 g/d in men and 25 g/d

Table 1. Description of Studies in the Analyses of Dietary Fiber and Colorectal Cancer in the Pooling Project

Study	Follow-up Time	Baseline Cohort, No.	Colorectal Cancer Cases, No.	Dietary Fiber Intake, g/d*	Median (10th–90th Percentile) Fiber Intake From, g/d		
					Cereals	Fruits	Vegetables
Men							
Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC)	1985-1999	26 987	321	19 (13-27)	12 (7-20)	2 (1-4)	4 (2-6)
Cancer Prevention Study II Nutrition Cohort (CPS2)	1992-1999	66 090	720	14 (9-22)	5 (3-9)	3 (1-6)	5 (3-9)
Health Professionals Follow-Up Study (HPFS)	1986-2000	47 766	597	21 (14-31)	5 (3-11)	4 (1-9)	7 (4-12)
Netherlands Cohort Study (NLCS)	1986-1993	58 279	646	27 (20-38)	11 (6-19)	3 (1-6)	4 (2-7)
New York State Cohort (NYSC)	1980-1987	30 363	492	28 (20-39)	6 (5-7)	6 (2-12)	14 (9-22)
Women							
Breast Cancer Detection Demonstration Project Follow-up Study (BCDDP)	1987-1998	41 987	436	13 (8-21)	5 (2-9)	3 (1-7)	3 (2-6)
Canadian National Breast Screening Study (CNBSS)	1980-2000	49 613	612	16 (10-24)	3 (2-5)	6 (4-11)	3 (1-7)
Cancer Prevention Study II Nutrition Cohort (CPS2)	1992-1999	74 053	479	13 (8-19)	4 (2-8)	3 (1-6)	4 (2-8)
Iowa Women's Health Study (IWHS)	1986-2001	34 588	1010	18 (12-26)	4 (2-8)	4 (2-8)	7 (4-11)
Netherlands Cohort Study (NLCS)	1986-1993	62 573	501	24 (18-32)	9 (5-15)	4 (2-7)	4 (2-7)
New York State Cohort (NYSC)	1980-1987	22 550	296	24 (17-33)	5 (4-6)	5 (2-10)	11 (7-18)
New York University Women's Health Study (NYUWHS)	1985-1998	13 258	127	14 (8-22)	3 (2-7)	4 (1-8)	5 (2-10)
Nurses' Health Study (a) (NHSa)	1980-1986	88 651	220	13 (8-20)	2 (1-4)	4 (1-8)	4 (2-8)
Nurses' Health Study (b) (NHSb)†	1986-2000	68 502	648	17 (12-24)	4 (2-7)	4 (1-8)	6 (3-10)
Prospective Study on Hormones, Diet, and Breast Cancer (ORDET)	1989-2001	9027	61	18 (13-23)	8 (5-11)	5 (2-9)	3 (2-6)
Swedish Mammography Cohort (SMC)	1987-2003	61 459	714	20 (14-27)	13 (7-19)	3 (1-7)	1 (1-3)
Women's Health Study (WHS)	1993-2002	38 384	201	17 (12-25)	4 (2-6)	3 (1-7)	6 (3-10)
Total		725 628	8081				

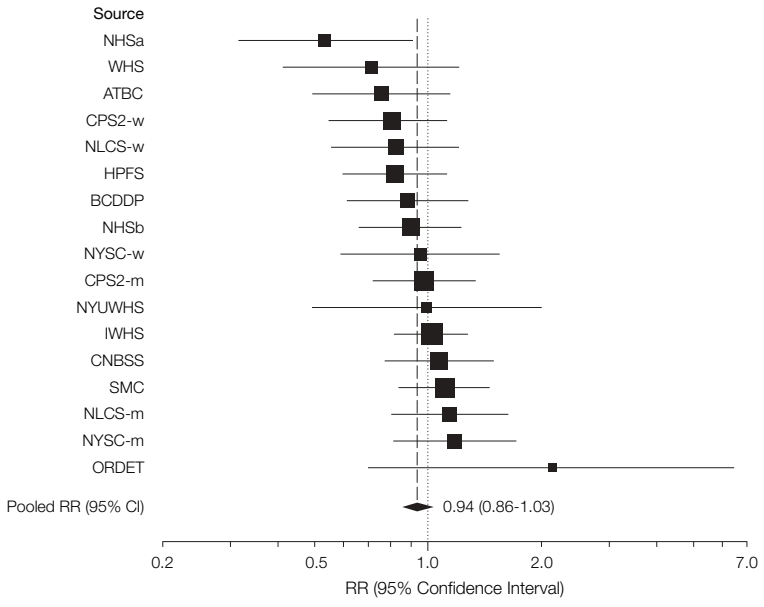
*Median and 10th-90th percentile intake.
†The NHSb is a subset of the NHSa and is not included in the total baseline cohort.

Table 2. Pooled Relative Risks of Colorectal Cancer for Quintiles of Dietary Fiber Intake

	Quintile*					*P* Value for Trend	*P* Value for Between-Studies Heterogeneity†	*P* Value for Between-Studies Heterogeneity Due to Sex†	*P* Value for Common Effects by Tumor Site†
	1	2	3	4	5				
Colorectal cancer (n = 8081)									
Age-adjusted	1.00	0.90 (0.84-0.97)	0.86 (0.79-0.94)	0.90 (0.84-0.97)	0.84 (0.77-0.92)	.002	.14	.66	
Multivariate I‡	1.00	0.91 (0.85-0.98)	0.88 (0.82-0.95)	0.93 (0.87-1.00)	0.88 (0.82-0.95)	.01	.38	.92	
Multivariate II§	1.00	0.92 (0.85-0.99)	0.90 (0.83-0.97)	0.96 (0.88-1.04)	0.92 (0.84-1.01)	.38	.31	.98	
Multivariate III‖	1.00	0.93 (0.86-1.00)	0.91 (0.84-0.98)	0.97 (0.90-1.05)	0.94 (0.86-1.03)	.75	.45	.74	
Colon cancer (n = 5726)									
Age-adjusted	1.00	0.91 (0.83-0.99)	0.86 (0.78-0.95)	0.91 (0.84-0.99)	0.87 (0.79-0.95)	.03	.31	.71	
Multivariate III‖	1.00	0.94 (0.86-1.03)	0.92 (0.83-1.02)	1.00 (0.91-1.10)	1.00 (0.90-1.11)	.40	.70	.83	
Rectal cancer (n = 2188)									
Age-adjusted	1.00	0.91 (0.80-1.04)	0.86 (0.75-0.98)	0.89 (0.77-1.01)	0.81 (0.71-0.93)	.03	.47	.81	.44
Multivariate III‖	1.00	0.93 (0.81-1.07)	0.89 (0.77-1.03)	0.93 (0.80-1.09)	0.85 (0.72-1.01)	.18	.52	.66	.07

*The quintiles were defined within each individual study using the subcohort for the 2 case-cohort studies (the Canadian National Breast Screening Study and the Netherlands Cohort Study) and the baseline cohort for the remaining studies.
†For quintile 5.
‡Adjusted for age; body mass index (calculated as weight in kilograms divided by the square of height in meters) (<23, 23-<25, 25-<30, ≥30; height (men: <1.70, 1.70-<1.75, 1.75-<1.80, 1.80-<1.85, ≥1.85 m; women: <1.60, 1.60-<1.65, 1.65-<1.70, 1.70-<1.75, ≥1.75 m); education (<high school graduate, high school graduate,>high school graduate); physical activity (low, medium, high); family history of colorectal cancer (no, yes); use of postmenopausal hormone therapy (premenopausal, never, ever); oral contraceptive use (never, ever); use of nonsteroidal anti-inflammatory drugs (no, yes); multivitamin use (no, yes <6 times/wk, yes ≥6 times/wk, yes missing dose for the Breast Cancer Detection Demonstration Project Follow-up Study, Health Professionals Follow-up Study, Iowa Women's Health Study, Nurses' Health Study [a and b], and Women's Health Study; no, yes, for the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, Cancer Prevention Study II Nutrition Cohort, Netherlands Cohort Study, and New York State Cohort); smoking habits (never, past [<20 y, 20-<40 y, ≥40 y], current [<25 cigarettes/d and <40 y, <25 cigarettes/d and ≥40 y, ≥25 cigarettes/d and <40 y, ≥25 cigarettes/d and ≥40 y]); and total energy (continuous).
§Multivariate I + intake of dietary folate (quintiles).
‖Multivariate II + intake of red meat (quintiles), total milk (quartiles), and alcohol (0, >0-<5, 5-<15, 15-<30, ≥30 g/d).

Figure 1. Study-Specific and Pooled Multivariate Relative Risks (RRs) of Colorectal Cancer Comparing the Highest vs the Lowest Quintile of Dietary Fiber Intake



The squares and horizontal lines correspond with the multivariate study-specific relative risks (RRs) and 95% confidence intervals (CIs), for the highest quintile of dietary fiber intake compared with the lowest. The relative risks were adjusted for the covariates listed in multivariate model III in Table 2. The size of a square reflects the study-specific weight (inverse of the variance), and the diamond represents the pooled relative risk and 95% confidence interval. The vertical dashed line represents the pooled relative risk. The abbreviations of the studies are listed in Table 1.

in women). The association between dietary fiber intake and risk of colorectal cancer was not significantly modified by sex or age at diagnosis; compared with the lowest quintile the pooled multivariate RR for the highest quintile was 0.96 (95% CI, 0.82-1.13) for men; 0.93 (95% CI, 0.83-1.04) for women; (*P* for between-studies heterogeneity due to sex = .74); 0.96 (95% CI, 0.82-1.12) for cases diagnosed in patients younger than age 65 years (3048 cases); and 0.92 (95% CI, 0.79-1.06) for patients diagnosed at age 65 years and older (5033 cases). We also found no statistically significant differences in the association between dietary fiber intake and colorectal cancer risk by body mass index (calculated as weight in kilograms divided by the square of height in meters), smoking, alcohol consumption, and red meat intake (data not shown). In addition, the results were similar in European and North American studies: the pooled multivariate RR in the highest quintile vs the lowest was 0.99 (95% CI, 0.80-1.23) for the European studies and 0.92 (95% CI, 0.83-

1.02) for the North American studies (*P* for difference = .45).

To examine whether the association between dietary fiber intake and risk of colorectal cancer was modified by length of follow-up, we performed separate analyses for cases diagnosed within the first 5 years of follow-up and for cases diagnosed at least 5 years after their baseline assessment. When follow-up time was limited to only the first 5 years, there was a suggestion of an inverse association (pooled multivariate RR = 0.87; 95% CI, 0.76-1.00 in the highest quintile vs the lowest; 3257 cases). However, after a 5-year latency period between the baseline diet assessment and outcome ascertainment, no association was observed (pooled multivariate RR = 1.00; 95% CI, 0.89-1.12 in the highest quintile vs the lowest; 4824 cases).

In categorical analyses using identical absolute intake cut points across studies, the pooled age-adjusted RR was 0.90 (95% CI, 0.75-1.08) and the pooled multivariate RR was 1.00 (95% CI, 0.85-1.17) (TABLE 3) for comparisons of dietary fiber intake of 30 or more g/d vs 10 to less than 15 g/d. However, the pooled multivariate RR was significantly elevated (RR = 1.18; 95% CI, 1.05-1.31) among individuals with dietary fiber intake less than 10 g/d (11% of the overall study population) compared with 10 to less than 15 g/d. Because the association between dietary fiber intake and risk of colorectal cancer was nonlinear, we calculated measurement error corrected RRs for comparisons of less than 10 g/d vs 10 or more g/d. For this comparison, the strongest confounder was smoking status. Among the studies that had colorectal cancer cases with dietary fiber intake of less than 10 g/d, measured smoking status, and had a sufficient range of dietary fiber intake in their validation study to perform the misclassification analysis, correction for misclassification of dietary fiber intake strengthened the association: the pooled age and smoking adjusted RR comparing less than 10 g/d vs 10 or more g/d of dietary fiber intake changed from 1.22 (95% CI, 1.10-1.35) to 2.16 (95% CI, 1.12-4.16) after correction for measurement error.

The nonparametric regression curve obtained after combining all studies into a single data set showed a pattern similar to the categorical analyses in which study-specific RRs were pooled (FIGURE 2): the multivariate RR declined with increasing dietary fiber intake up to about 15 g/d, but then flattened out (*P* for nonlinearity = .05).

There was a suggestion that the association with dietary fiber intake differed by tumor site (*P* for common effects by tumor site for the highest quintile = .07) (Table 2). Comparing the highest vs lowest quintile of intake, a

Table 3. Pooled Relative Risks of Colorectal Cancer for Categories of Dietary Fiber Intake

	Dietary Fiber Intake, g/d						*P* Value for Trend	*P* Value for Between-Studies Heterogeneity*	*P* Value for Between-Studies Heterogeneity Due to Sex*
	<10	10-<15	15-<20	20-<25	25-<30	≥30			
Colorectal cancer†									
No. of cases	609	1681	2263	1740	1001	785			
Person-years	513 317	1 591 322	1 870 758	1 183 334	514 142	313 572			
Age-adjusted	1.27 (1.15-1.40)	1.00	0.99 (0.93-1.06)	0.95 (0.87-1.03)	0.90 (0.80-1.01)	0.90 (0.75-1.08)	.18	.15	.05
Multivariate‡	1.18 (1.05-1.31)	1.00	1.02 (0.95-1.10)	1.01 (0.92-1.10)	0.99 (0.87-1.12)	1.00 (0.85-1.17)	.68	.54	.22
Colon cancer†									
No. of cases	430	1203	1620	1223	711	537			
Person-years	513 311	1 591 290	1 870 713	1 183 264	514 073	313 513			
Age-adjusted	1.24 (1.11-1.40)	1.00	1.00 (0.92-1.08)	0.94 (0.85-1.04)	0.94 (0.83-1.07)	0.90 (0.73-1.12)	.44	.18	.02
Multivariate‡	1.17 (1.03-1.34)	1.00	1.04 (0.95-1.13)	1.03 (0.93-1.15)	1.08 (0.93-1.25)	1.04 (0.86-1.26)	.17	.83	.10
Rectal cancer§	<10	10-<15	15-<20	20-<25	≥25				
No. of cases	159	427	576	452	417				
Person-years	505 039	1 589 654	1 853 445	1 141 533	672 692				
Age-adjusted	1.35 (1.11-1.64)	1.00	0.98 (0.84-1.14)	0.96 (0.78-1.18)	0.85 (0.70-1.04)		.17	.77	.58
Multivariate‡	1.18 (0.82-1.68)	1.00	1.00 (0.86-1.17)	0.96 (0.80-1.15)	0.87 (0.68-1.09)		.27	.67	.77

*For the highest category.

†For the colorectal and colon cancer analyses, the Netherlands Cohort Study and the New York State Cohort were excluded from the <10 g/d category because these studies did not have any cases in that category; ORDET was excluded from the ≥30 g/d category because this study did not have any cases in that category.

‡Adjusted for age; body mass index (calculated as weight in kilograms divided by the square of height in meters) (<23, 23-<25, 25-<30, ≥30; height (men: <1.70, 1.70-<1.75, 1.75-<1.80, 1.80-<1.85, ≥1.85 m; women: <1.60, 1.60-<1.65, 1.65-<1.70, 1.70-<1.75, ≥1.75 m); education (<high school graduate, high school graduate, >high school graduate); physical activity (low, medium, high); family history of colorectal cancer (no, yes); use of postmenopausal hormone therapy (premenopausal, never, ever); oral contraceptive use (never, ever); use of nonsteroidal anti-inflammatory drugs (no, yes); multivitamin use (no, yes <6 times/wk, yes ≥6 times/wk, yes missing dose for the Breast Cancer Detection Demonstration Project Follow-up Study, Health Professionals Follow-up Study, Iowa Women's Health Study, Nurses' Health Study [a and b], and Women's Health Study; no, yes, for the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, Cancer Prevention Study II Nutrition Cohort, Netherlands Cohort Study, and New York State Cohort); smoking habits (never, past [<20y, 20-<40y, ≥40 y], current [<25 cigarettes/d and <40 y, <25 cigarettes/d and ≥40 y, ≥25 cigarettes/d and <40 y, ≥25 cigarettes/d and ≥40 y]; alcohol (0 g/d, >0-<5 g/d, 5-<15 g/d, 15-<30 g/d, ≥30 g/d); dietary intake of folate (quintiles), red meat (quintiles), total milk (quartiles), and total energy (continuous).

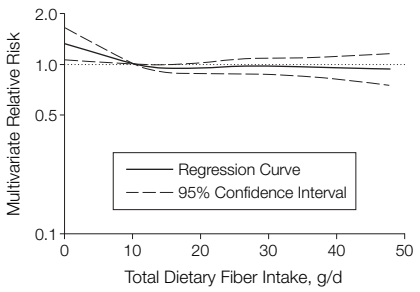
§For the rectal cancer analyses, the highest category of dietary fiber intake is defined as ≥25 g/d due to small numbers of cases with higher intakes. For the rectal cancer analyses, the Netherlands Cohort Study, New York State Cohort, and ORDET were excluded from the <10 g/d category because these studies did not have any cases in that category; the Cancer Prevention Study II Nutrition Cohort was excluded from the ≥25 g/d category because this study did not have any cases in that category; and the male cohort of the New York State Cohort was excluded from the rectal cancer analyses because this study had no cases in the reference group.

null association was found for colon cancer (pooled multivariate RR=1.00; 95% CI, 0.90-1.11), whereas a borderline-significant, weak inverse association was found for rectal cancer (pooled multivariate RR=0.85; 95% CI, 0.72-1.01). Further analyses of proximal colon cancer (pooled multivariate RR=1.05; 95% CI, 0.91-1.21) and distal colon cancer separately (pooled multivariate RR=0.96; 95% CI, 0.80-1.14) showed no statistically significant association (*P* for common effects by tumor site for the highest quintile=.24).

In analyses of the sources of dietary fiber, fiber intakes from cereals and fruits were each associated with approximately a 10% reduction in risk of colorectal cancer in the age-adjusted model comparing the highest quintile with the lowest (TABLE 4). However, after adjustment for potential colorectal cancer risk factors, the associations were attenuated and not statistically significant (pooled multivariate RR=1.00; 95% CI, 0.93-1.08 for fiber from cereals; pooled multivariate RR=0.96; 95% CI, 0.89-1.04 for fiber from fruits in the highest quintile vs the lowest). Dietary fiber from vegetables was not associated with risk of colorectal cancer in both the age-adjusted and multivariate models. When associations with specific sources of dietary fiber were examined by tumor site, we found that the associations with fiber intake from cereals were significantly different between colon and rectal cancer (*P* for common effect by tumor site for the highest quintile=.05), even though neither association was statistically significant. Comparing the highest vs the lowest quintile for fiber intake from cereals, the pooled multivariate RR was 0.91 (95% CI, 0.78-1.06, *P* for trend=.20) for rectal cancer, and 1.03 (95% CI, 0.94-1.13, *P* for trend=.90) for colon cancer. For fiber intake from fruits and from vegetables, no significant differences by tumor site were observed (data not shown).

Intakes of whole grain and refined grain food were each not statistically associated with risk of colorectal cancer: the pooled multivariate RR in the highest quintile vs the lowest were 0.92 (95% CI, 0.84-1.00, *P* for trend=.21) for whole grain food and 1.01 (95% CI, 0.91-1.13, *P* for trend=.94) for refined grain food. Although the results did not significantly differ by tumor site for both whole and refined grain food intake, there was a suggestion that whole grain food intake was inversely associated with risk of rectal cancer (pooled multivariate RR=0.81; 95% CI, 0.65-1.00 in the highest quintile vs the lowest, *P* for trend=.07). In the analyses of grain foods, if dietary folate intake was not included as a covariate, the results did not change.

Figure 2. Nonparametric Regression Curve for the Association Between Dietary Fiber Intake and Risk of Colorectal Cancer



COMMENT

In this pooled analysis of 13 prospective cohort studies, we observed a statistically significant inverse association between dietary fiber intake and risk of colorectal cancer in the age-adjusted model. However, the overall association was attenuated and no longer statistically significant after ad-

Table 4. Pooled Relative Risks of Colorectal Cancer by Sources of Dietary Fiber Intake

Fiber Source	Quintile* 1	2	3	4	5	*P* Value for Trend	*P* Value for Between-Studies Heterogeneity†	*P* Value for Between-Studies Heterogeneity Due to Sex†
Cereals								
Age-adjusted	1.00	0.94 (0.87-1.02)	0.94 (0.87-1.01)	0.93 (0.86-1.00)	0.90 (0.83-0.97)	.001	.20	.23
Multivariate‡	1.00	0.97 (0.90-1.05)	1.00 (0.93-1.08)	1.01 (0.94-1.09)	1.00 (0.93-1.08)	.57	.71	.53
Fruits								
Age-adjusted	1.00	0.96 (0.90-1.03)	0.90 (0.84-0.97)	0.90 (0.83-0.96)	0.88 (0.81-0.96)	.004	.23	.55
Multivariate‡	1.00	0.99 (0.92-1.07)	0.95 (0.88-1.02	0.96 (0.89-1.03)	0.96 (0.89-1.04)	.30	.75	.15
Vegetables								
Age-adjusted	1.00	0.97 (0.88-1.06)	0.92 (0.84-1.00)	0.91 (0.84-0.99)	0.97 (0.90-1.05)	.39	.24	.66
Multivariate‡	1.00	0.98 (0.90-1.07)	0.95 (0.87-1.02)	0.95 (0.87-1.03)	1.02 (0.94-1.11)	.58	.71	.75

*The quintiles were defined within each individual study using the subcohort for the 2 case-cohort studies (the Canadian National Breast Screening Study and the Netherlands Cohort Study) and the baseline cohort for the remaining studies.
†For highest quintile.
‡Adjusted for age; body mass index (calculated as weight in kilograms divided by the square of height in meters) (<23, 23-<25, 25-<30, ≥30; height (men: <1.70, 1.70-<1.75, 1.75-<1.80, 1.80-<1.85, ≥1.85 m; women: <1.60, 1.60-<1.65, 1.65-<1.70, 1.70-<1.75, ≥1.75 m); education (<high school graduate, high school graduate,>high school graduate); physical activity (low, medium, high); family history of colorectal cancer (no, yes); use of postmenopausal hormone therapy (premenopausal, never, ever); oral contraceptive use (never, ever); use of nonsteroidal anti-inflammatory drugs (no, yes); and multivitamin use (no, yes <6 times/wk, yes ≥6 times/wk, yes missing dose for the Breast Cancer Detection Demonstration Project Follow-up Study, Health Professionals Follow-up Study, Iowa Women's Health Study, Nurses' Health Study [a and b], and Women's Health Study) no, yes, for the Alpha-Tocopherol Beta Carotene Cancer Prevention Study, Cancer Prevention Study II Nutrition Cohort, Netherlands Cohort Study, and New York State Cohort); smoking habits (never, past [<20 y, 20-<40 y, ≥40 y], current [<25 cigarettes/d and <40 y, <25 cigarettes/d and ≥40 y, ≥25 cigarettes/d and <40 y, ≥25 cigarettes/d and ≥40 y]); alcohol (0 g/d, >0-<5 g/d, 5-<15 g/d, 15-<30 g/d, ≥30 g/d); dietary intake of folate (quintiles), red meat (quintiles), total milk (quartiles), and total energy (continuous).

justing for other colorectal cancer risk factors. When intakes of dietary fiber were examined separately by specific food sources, none were associated with risk of colorectal cancer. However, there was a suggestion that intake of dietary fiber from cereals and intake of dietary fiber from whole grain foods were both associated with a weak reduction in risk of rectal cancer.

The association between dietary fiber intake and risk of colorectal cancer has been inconsistent among observational studies and several factors may explain the disparity: potential biases in each study, the failure to adjust for covariates in the multivariate models, and the range of dietary fiber intake. Inconsistent results also have been reported from randomized clinical trials of dietary fiber supplementation on the recurrence of colorectal adenomas (precursors of colorectal cancer); most trials have found no reduced risk of adenoma recurrence with dietary fiber supplementation compared with placebo,[9-12] but one trial found a significantly increased risk of adenoma recurrence in the psyllium supplementation group.[48]

A statistically significant reduction in risk of colorectal cancer with higher dietary fiber intake has been observed in most case-control studies.[49] However, case-control studies are prone to recall bias because dietary assessments are obtained after cancer diagnosis and also are prone to selection bias because control participants who participate are likely to be particularly health-conscious. In addition, publication bias may contribute to the accumulation of literature with significant findings. On the other hand, the Pooling Project is less susceptible to these biases because diet was assessed prior to diagnosis and the studies were not required to have published on the association between dietary fiber intake and risk of colorectal cancer.

The etiology of colorectal cancer has been studied extensively during the past few decades leading to the identification of many risk factors for colorectal cancer. Because earlier case-control studies did not adjust for recently identified colorectal cancer risk factors, reported associations with dietary fiber may have been confounded by factors for which no adjustment was made in the multivariate models. The different results observed among recent studies also may be explained, in part, by the selection of the covariates that were included in the multivariate models. Recently the EPIC study, a multicenter prospective cohort study with 10 European countries (n=519 978; 1721 cases), found a statistically significant 30% lower risk of colorectal cancer in the multivariate model adjusted for age, sex, weight, height, nonfat energy, energy from fat, and center (RR=0.70; 95% CI, 0.58-0.85 in the highest quintile vs the lowest).[13] Additional adjustment for folate intake did not change the result (RR=0.68; 95% CI, 0.55-0.84), but noticeable attenuation was observed (RR=0.79; 95% CI, 0.63-0.99) after adjusting for other risk factors such as education, physical activity, alcohol, smoking, and red meat intake. In the Pooling Project, the inverse association observed between dietary fiber intake and risk of colorectal cancer in the age-adjusted model (RR=0.84; 95% CI, 0.77-0.92) (Table 2) was attenuated after adjusting for age, nondietary risk factors, multivitamin use, and energy intake, but remained statistically significant (pooled multivariate RR=0.88; 95% CI, 0.82-0.95) (Table 2, multivariate model I). However, further attenuation occurred after adjusting for dietary folate intake (pooled multivariate RR=0.92; 95% CI, 0.84-1.01) (Table 2, multivariate model II), but no observable attenuation was observed after adjusting for other dietary factors such as consumption of red meat, total milk, and alcohol intake (pooled multivariate RR=0.94; 95% CI, 0.86-1.03) (Table 2, multivariate model III). In our study, intake of folate was positively correlated with intake of dietary fiber, while intakes of red meat and total milk were inversely correlated with intake of dietary fiber, but the strength of correlations varied across studies. Intake of alcohol was positively correlated with intake of dietary fiber in some studies, but showed an inverse correlation in other studies. Because the degree of confounding by other risk factors of colorectal cancer may vary depending on characteristics of a study population, thorough examination for selection of covariates to be included in a multivariate model is needed.

The range of dietary fiber intake reported within a study may be another factor that has contributed to different findings among studies. If the range of intake of a nutrient in a study is very narrow, a null association may be more likely observed. However, lack of variation in dietary fiber intake is unlikely to have accounted for the null association we found. In our analyses, the study-specific mean energy-adjusted dietary fiber intake was 9 to 20 g/d for men and 8 to 17 g/d for women in the lowest quintile and 23 to 41 g/d for men and 20 to 35 g/d for women in the highest quintile with a 1.8- to 3.0-fold difference in intakes between the 2 extreme quintiles across studies. This range is similar to the range observed in EPIC, which reported a statistically significant inverse association with dietary fiber intake. Mean dietary fiber intake in EPIC was 18 g/d for men and 16 g/d for women in the lowest quintile and 30 g/d for men and 24 g/d for women in the highest quintile (a 1.5- to 1.7-fold difference).[13] In addition, when we used identical absolute intake cut points across studies, no association was observed for dietary fiber intake of at least 30 g/d vs 10 to less than 15 g/d, which is similar to the quintile definitions used in EPIC.

Because the Pooling Project is a retrospectively planned pooled analysis of the primary data, the food frequency questionnaires that were used to assess diet varied across studies. To take into account potential misclassification in dietary fiber intake that may arise from measurement error in energy intake, we calculated energy-adjusted intakes for each study. We also conducted analyses by categorizing dietary fiber intake using study-specific quin-

tiles and identical absolute intake cut points across studies. In the study-specific quintile analyses, true differences in population intakes were not taken into account, potentially resulting in misclassification of dietary fiber intake in the pooled results. However, misclassification could also have occurred in the analyses based on identical absolute intake cut points because dietary fiber intakes may vary across studies due to differences in the accuracy in which the food frequency questionnaires estimated dietary fiber. Despite the different potential for misclassification between these 2 analytic approaches, both showed no association between dietary fiber intake and risk of colorectal cancer above the lowest category of dietary intake.

Several limitations of our analysis should be considered. Fiber intake is likely to be measured with error because of errors in how study participants estimate their consumption of fiber-containing foods and by errors in the food composition databases. A true association between dietary fiber intake and risk of colorectal cancer may be underestimated in our study. In addition, although we were able to correct for misclassification of dietary fiber intake at baseline, the single assessment of dietary fiber intake in our analysis may not reflect long-term usual intake as accurately as using repeated measurements of dietary intake during follow-up. However, use of repeated measurements of dietary fiber intake in the Nurses' Health Study did not change substantially the risk estimates obtained from using baseline data only.[50] Because dietary fiber intake was assessed only at baseline, we also could not examine the effects of dietary fiber intake during earlier life periods (eg, childhood or young adulthood) or lifelong fiber intake on risk of colorectal cancer. Although misclassification in fiber intake also may have occurred because we did not have information on the use of dietary fiber supplements, a recent US national survey found that the prevalence of nonvitamin/nonmineral supplement use, including fiber supplements, was less than 4%.[51] Therefore, failure to measure use of fiber supplements is unlikely to have led to substantial misclassification of dietary fiber intake.

A strength of the Pooling Project is that the individual data from each cohort were reanalyzed using a standard approach, which provided more flexibility in examining dose-response relationships, confounding, and effect modification than meta-analyses of the published literature, which frequently summarize risk estimates obtained for heterogeneous exposure categories with different adjustment for potential confounders. Also, we had high statistical power with over 8000 colorectal cancer cases, thus a substantial effect of fiber is unlikely to have been missed. In addition, in a subset of the studies we were able to correct for measurement error in dietary fiber intake using their validation study data. Our ability to correct for measurement error strengthened the estimated association observed between very low dietary fiber intake and colorectal cancer risk; however, it should be noted that in this analysis we could only adjust for age and smoking, the 2 strongest confounders in the multivariate analysis when comparing less than 10 vs 10 g/d or more of dietary fiber intake.

In conclusion, we did not find support for a linear inverse association between dietary fiber intake and risk of colorectal cancer in a pooled analysis of 13 prospective cohort studies. Although high dietary fiber intake may not have a major effect on the risk of colorectal cancer, a diet high in dietary fiber from whole plant foods can be advised because this has been related to lower risks of other chronic conditions such as heart disease and diabetes.[52]

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